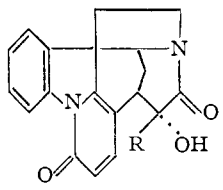
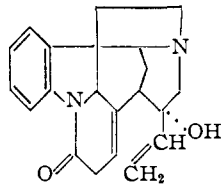
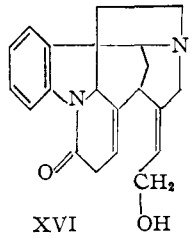


XIV



XV

binol (XV) (*hydrochloride*, m.p. 195–205° dec., calcd. for $C_{21}H_{22}O_2N_2Cl\cdot 2H_2O$: C, 61.97; H, 6.69; N, 6.89. Found: C, 61.87; H, 6.97; N, 6.97), which was rearranged by hydrogen bromide in acetic acid, followed by boiling aqueous sulfuric acid, to isostrychnine I (XVI)[2] (m.p. [evacuated tube] 229–230°, $[\alpha]^{22}D$ +23 ± 4° (c = 2.54 [EtOH])), identical in all respects with an authen-



XVI

tic sample (m.p. [evacuated tube] 228–230°, $[\alpha]^{25}D$ +25 ± 4° (c = 2.44 [EtOH])), and further characterized through isomerization by ethanolic potash[3] to strychnine (I), identical in infrared spectrum, melting point, and chromatographic behavior with the natural alkaloid.

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RECEIVED AUGUST 23, 1954

(2) H. Leuchs and H. Schulte, *Ber.*, **75**, 1522 (1942).

(3) V. Prelog, J. Battegay and W. I. Taylor, *Helv. Chim. Acta*, **31**, 2244 (1948).

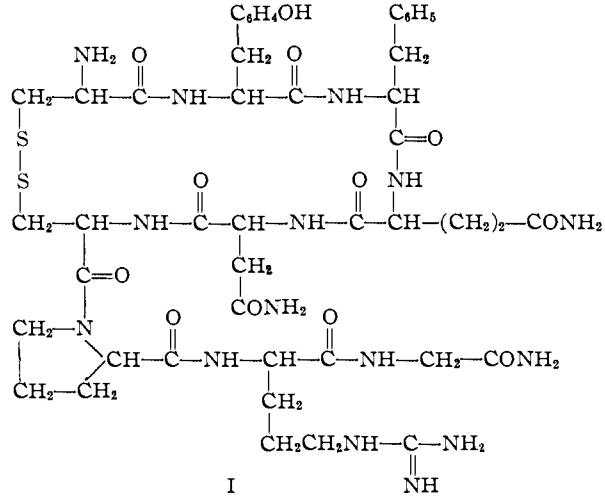
(4) On leave of absence from the University, Bristol, England.

A SYNTHETIC PREPARATION POSSESSING BIOLOGICAL PROPERTIES ASSOCIATED WITH ARGININE-VASOPRESSIN

Sir:

In a recent Communication[1] on the structures of arginine-vasopressin and lysine-vasopressin it was recorded in a footnote that a synthesis by du Vigneaud, Popenoe and Roeske of the octapeptide structure proposed for lysine-vasopressin had led to biologically active material. As this work continued, the synthesis of arginine-vasopressin was undertaken.

The present Communication is concerned with the preparation and partial purification of a product synthesized according to the structure (I) proposed for arginine-vasopressin.[1,2] The synthesis was approached through the preparation of the appropriate benzylated cysteine-containing nonapeptide, N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide (II), debenzylation of this compound with sodium in liquid ammonia and cyclization of the resulting sulfhydryl nonapeptide to the disulfide. Synthesis of II was accomplished by coupling N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine (III) with S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide monohydrobromide (IV).



I

L-Phenylalanyl-L-glutaminyl-L-asparagine[3] was coupled with N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosine[4] by the isobutyl chlorocarbonate mixed anhydride procedure[5] to give III, m.p. 208–209°, $[\alpha]^{22}D$ −26° (c 1, dimethylformamide) (calcd. for $C_{45}H_{51}O_{11}N_7S$: C, 60.2; H, 5.72; N, 10.9; S, 3.57. Found: C, 59.9; H, 5.77; N, 10.4; S, 3.57).

N^{α}-*p*-Nitrobenzyloxycarbonyl-L-arginylglycinamide was prepared by the procedure of Gish and Carpenter[6] and isolated as the picrate (V), m.p. 168–171°, $[\alpha]^{22}D$ −3.8° (c 1, acetone–water (4:1)) (calcd. for $C_{16}H_{23}O_6N_7\cdot C_6H_3O_7N_3$: C, 41.4; H, 4.10; N, 21.9. Found: C, 41.4; H, 4.17; N, 21.8). V was treated with HBr–acetic acid and the reaction product isolated as the monohydrobromide (VI).

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteine, m.p. 132.5–133°, $[\alpha]^{22}D$ −47.0° (c 1, 95% ethanol) (calcd. for $C_{18}H_{18}O_6N_2S$: N, 7.18; S, 8.21. Found: N, 7.05; S, 8.03), as its acid chloride was condensed with proline benzyl ester. Saponification of the peptide ester gave S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline (VII) as an oil (neut. equiv., calcd., 487.5. Found, 487).

VI was condensed with VII by the pyrophosphite method[7] to give S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-prolyl-L-arginylglycinamide hydrobromide (VIII) characterized as the picrate, m.p. 182–185°, $[\alpha]^{22}D$ −47.7° (c 1, acetone–water (4:1)) (calcd. for $C_{31}H_{41}O_8N_9S\cdot C_6H_3O_7N_3$: C, 47.8;

(1) V. du Vigneaud, H. C. Lawler and E. A. Popenoe, THIS JOURNAL, **75**, 4880 (1953).

(2) R. Archer and J. Chauvet, *Biochim. et Biophys. Acta*, **12**, 487 (1953).

(3) E. A. Popenoe and V. du Vigneaud, THIS JOURNAL, in press.

(4) C. R. Harington and R. V. Pitt Rivers, *Biochem. J.*, **38**, 417 (1944).

(5) J. R. Vaughan, Jr., and J. A. Eichler, THIS JOURNAL, **75**, 5556 (1953).

(6) D. T. Gish and F. H. Carpenter, *ibid.*, **75**, 5872 (1953).

(7) G. W. Anderson, J. Blodinger and A. D. Welcher, *ibid.*, **74**, 5309 (1952).

H, 4.77; N, 18.1. Found: C, 47.8; H, 4.95; N, 17.7). VIII was treated with HBr–acetic acid and the reaction product isolated as the monohydrobromide (IV).

Compounds III and IV were coupled by the pyrophosphite method and ether added to the reaction mixture. The resulting precipitate was dried and treated with sodium in liquid ammonia. The product in dilute aqueous solution at *p*H 6.7 was aerated and the solution concentrated and lyophilized. The material from several runs upon assay[8] gave a total of 58,000 units of pressor activity. After purification by countercurrent distribution, the active material [K = 0.84 (*sec*-butyl alcohol–*p*-toluenesulfonic acid)] was subjected to electrophoresis in a pyridine–acetic acid buffer ($p\mathrm{H}_4$) on a cellulose-supporting medium.[9] The solution from the segment with peak activity assayed 15,500 pressor units and when lyophilized yielded a powder weighing 37 mg. which indicated a specific activity in solution of 400 units/mg. However, the material suffered partial inactivation[10] upon lyophilization, assaying 175 units/mg.

In countercurrent distribution, electrophoresis and chromatography on partition and ion-exchange columns, the position of the activity of this final synthetic product was the same as that of the natural arginine-vasopressin. In addition to the assays against the U.S.P. Standard Powder for pressor activity, the product was assayed for antidiuretic[11] and avian vasodepressor[12] activities. The ratios between the pressor, antidiuretic and avian vasodepressor activities were the same as those found for natural vasopressin (1:1:0.15).

Further studies on the purification of the synthetic product are underway and it is hoped that an extensive comparison of its chemical and physical properties with those of natural arginine-vasopressin may eventually be carried out. Since the difficulties are considerable in reaching and maintaining maximum activity, it was felt that a report was warranted at the present time that a synthetic product synthesized according to the structure proposed for arginine-vasopressin (I) does possess the expected biological properties.

DEPARTMENT OF BIOCHEMISTRY VINCENT DU VIGNEAUD[13]
CORNELL UNIV. MEDICAL COLLEGE DUANE T. GISH[14]
NEW YORK, N. Y. PANAYOTIS G. KATSOYANNIS[15]

RECEIVED AUGUST 5, 1954

(8) J. Dekanski, *Brit. J. Pharmacol.*, **7**, 567 (1952).

(9) H. G. Kunkel in "Methods of Biochemical Analysis," Vol. I, D. Glick, Ed., Interscience Publishers, Inc., New York, N. Y., p. 141.

(10) Samples of highly purified natural vasopressin have also on some occasions shown a loss in activity on concentration and lyophilization [R. A. Turner, J. G. Pierce and V. du Vigneaud, *J. Biol. Chem.*, **191**, 21 (1951); E. A. Popenoe and V. du Vigneaud, *J. Biol. Chem.*, **205**, 133 (1953)]. Studies are underway to determine the cause as well as to find means of avoiding such inactivation.

(11) The antidiuretic assays utilizing the hydrated normal dog were carried out by Professor H. B. van Dyke, Dr. K. Adamsons, Jr., and Mr. S. L. Engel, to whom we express our appreciation.

(12) J. M. Coon, *Arch. intern. pharmacodynamie*, **62**, 79 (1939).

(13) Appreciation is expressed to the Lederle Laboratories Division, American Cyanamid Company, for a research grant which has aided greatly in this study.

(14) Lilly Postdoctoral Fellow in the Natural Sciences, National Research Council.

(15) Fellow of State Scholarships Foundation of Greece.

BOOK REVIEWS

Dictionary of Organic Compounds, 4 Volumes. By SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.I.C., F.R.S., and H. M. BUNBURY, M.Sc., F.R.I.C. Oxford University Press, 114 Fifth Avenue, New York 11, N. Y. 1954. Volume I, xvi + 654 pp.; Volume II, xvi + 845 pp.; Volume III, xvi + 838 pp.; Volume IV, xvi + 694 pp.; Each Volume—20 × 27 cm. Price, $78.00 a set.

During the past twenty years Heilbron's "Dictionary of Organic Compounds" has become a standard reference work for chemists concerned with organic compounds. This dictionary has proved especially valuable in connection with research and courses involving the characterization of organic compounds. For these reasons it is fortunate that this valuable reference work has been revised and brought up to date. Over 2500 new entries are included in this revised edition. In addition, the original entries have been brought up to date to the end of 1950 and in some cases to 1953. After a random check of some of the compounds with which this reviewer is familiar it appears that the revision has indeed been comprehensive. The earlier data have in many instances been replaced or supplemented by more accurate and recent data.

The style and format are essentially the same as in the original edition. The compounds are arranged in alphabetical order and each entry contains the following information: structural and molecular formulas, physical properties including solubilities, characteristic chemical properties, functional derivatives and principal references. Ambiguities which might be anticipated with an alphabetical classification have been minimized by the liberal use of cross references and by carefully stating the nomenclature rules in the introduction.

Although Heilbron's "Dictionary of Organic Compounds" is not as comprehensive as Beilstein or Elsevier's "Encyclopedia of Organic Chemistry," and by no means is intended to be, it offers the advantage of being more up to date and convenient to use.

The editors deserve praise for their efforts in making this revised edition available.

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General Biochemistry. By WILLIAM H. PETERSON, Ph.D., Emeritus Professor of Biochemistry, University of Wisconsin, Madison, and FRANK M. STRONG, Ph.D., Professor of Biochemistry, University of Wisconsin, Madison. Prentice–Hall, Inc., Englewood Cliffs, New Jersey. 1953. v + 469 pp. 15.5 × 23.5 cm. Price, $8.65.

Modern biochemistry owes its origins to two sources, agriculture and medicine, and has been nourished and sustained by numerous developments in the fundamental sciences of biology, chemistry and physics. Few scientific areas in recent times include so broad a scope of activity